SYNTHESIS OF SUBSTITUTED AMINOQUINOLINES AS USEFUL INTERMEDIATES FOR PREPARATION OF AROMATIC N-TRICYCLIC SYSTEMS

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Abstract – An effective approach for the synthesis of new substituted mono and diaminoquinolines is described. Two known quinolines 7,8-dichloro-6-nitroquinoline (1) and 7,8-dichloro-6-nitrohydroquinolin-4-one (9) were used as key intermediates.

INTRODUCTION

Quinoline ring is well present in natural and synthetic compounds endowed with biological activities. Nevertheless, its chemistry continues to drawn the attention of many researchers over the world. Several reviews emphasises both synthetic approaches and reactivity of this heterocycle1-3 and a well documented application of the pharmacological properties of its derivatives is widely reported.4,5 Its outstanding importance from the medicinal chemistry point of view spans from the antimalarial drugs to the most recent wide spectrum antibacterial quinolones.6 In this context, in the past, some of us reported the synthesis of both novel triazolo[4,5-f]quinolines7 and their anticancer activity8 and triazolo[4,5-f] and [4,5-h]quinolinone carboxylic acids as antimicrobial analogues of oxolinic acid9,10 as well as we investigated on the synthesis and reactivity of some nitroquinolines.11 From these studies we were able to perform versatile procedures to afford 6,7-diaminoquinolines, 7-chloro-6-nitroquinolines and 6-aminoquinolines which allowed us to prepare novel triazolo[4,5-g]quinolines,12 imidazo[4,5-g]quinolines,12,13 pyrido[2,3-g]quinoxalines12-14 and [4,7]phenanthrolines.15 Now, in connection with these works we required new quinoline derivatives to use as synthons in the building up of novel tricyclic ring systems. This fact forced us to optimize the synthesis of the previously described12 8-chloro-6,7-diaminoquinoline (5) and 6,7-diaminoquinoline (7) of Scheme 1 and to obtain the new quinolines of Scheme 2.
RESULTS AND DISCUSSION

Our previous work\textsuperscript{12} on the preparation of the diamine (5) followed a similar scheme as that indicated below (Scheme 1). Compound (1) was converted into the intermediate (4) by ammonia in ethanol in a sealed vessel. Catalytic hydrogenation (10\% palladised charcoal and hydrogen) of the nitro group was conditioned upon the temperature of reaction. Thus, at room temperature, compound (5) was uniquely obtained in 90\% yield, whereas operating at 60°C compound (7) was isolated in 50\% yield and in this case hydrogenolysis of chlorine atom at 8 position occurred.\textsuperscript{12} In a preceding paper\textsuperscript{11} we could observe the different reactivity of chlorine atom in ortho to a nitro group in the quinoline ring when we attempted at obtaining the 3-methyl-3\textit{H}-triazolo[4,5-\textit{f}] or [4,5-\textit{g}]quinoline by reaction of 6-chloro-5-nitroquinoline or 6-chloro-7-nitroquinoline with methylhydrazine respectively. In that case only the 6-chloro-5-nitroquinoline reacted with methylhydrazine to give rise to a mixture of 3-methyltriazolo[4,5-\textit{f}]quinoline-1-oxide and 2-methyltriazolo[4,5-\textit{f}]quinoline-1-oxide in 5.4:1 ratio, while 6-chloro-7-nitroquinoline did not yield the expected ring closure but instead produced the sole reduction of the nitro group to a primary amine.

![Scheme 1](image)

With this in mind we have investigated the role played by these different bases in the reaction with compound (1) using the conditions depicted in Scheme 1. Thus, we have found a new procedure to obtain the 6-aminquinoline (6) that is not easy to prepare by a straightforward method because of the difficulty
of introducing a precursor nitro group selectively in this position by a nitrating agent. Our experiments show that when hydrazine hydrate in ethanol was used in the presence of 10% Pd/charcoal under reflux for 3h, compound (6) was obtained in 95% yield with total displacement of the chlorine atoms. Conversely the use of methyhydrazine in ethanol at 100°C for 80 h in a sealed vessel at 100°C yielded 60% of compound (2).

Scheme 2

Under the latter same conditions from 4 we obtained compound (5) in 95% yield. Analogously, from compound (4), under the conditions experienced in the case of 1, we isolated compound (7) in 70% yield with a similar displacement of chlorine atom. Compounds (2) and (5) were converted in mono (3) and
diacetyl (8) derivatives in very high yields. In our opinion the acquisition of compounds (6,7) operating with hydrazine in refluxing ethanol in the presence of a catalytic amount of Pd represents a new convenient procedure for preparation of monoamino and diaminoquinolines where methylhydrazine in the absence of catalyst acts only as a reducing agent. A similar behaviour was observed in the case of the previously described14 compound (9) when submitted to reaction with methylhydrazine in ethanol at 100°C in a sealed vessel which was converted into the amine (10) in 70% yield (Scheme 2). Similarly from compound (14), under the above conditions, compound (16) was selectively obtained in 80% yield. Not surprisingly ethylation of (9) with diethyl sulfate occurred at oxygen to give (11) thus demonstrating that the tautomeric equilibrium is prevailing as it is generally observed in the case of reaction with POCl₃. In fact either compound (14) or (16) were chlorinated at C-4. However, we must point out that 4-ethoxy group in (11) is easier displaced by ammonia in ethanol solution than the chlorine at C-7 and gives rise to a mixture of monoamino (13) and diamino (12) derivatives while in compound (15) nucleophilic displacement of chlorine to give (12) is almost quantitative (97%). An identical result (90-95% yield) was obtained starting from (11) and (13) running the same reaction for a prolonged time. These results represent an improvement in preparation of monoamino and diaminoquinolines for our work in progress.

EXPERIMENTAL

Melting points are uncorrected and were taken in open capillaries in a Digital Electrothermal IA9100 melting point apparatus. ¹H-NMR spectra were recorded at 200 MHz using a Varian XL-200 spectrometer. Chemical shifts are reported in ppm (δ) relative to tetramethylsilane as internal standard. MS spectra were performed on a combined HP 5790 (GC)-HP 5970 (MS) apparatus or with a combined Liquid Chromatograph-Agilent 1100 series Mass Selective Detector (MSD). Column chromatography was performed using 70-230 mesh (Merck silica gel 60). The progress of the reactions and the purity of the final compounds were monitored by TLC using Merck F-254 commercial plates.

Intermediates

7,8-Dichloro-6-nitroquinoline (1) and 7,8-dichloro-6-nitrodihydroquinolin-4-one (9) were known and they were prepared as previously reported12,14.

Reduction reactions

Method A: using methylhydrazine.

A solution of 1, 4, 9 or 14 (12.0 mmol) and methylhydrazine (3 mL) in 120 mL of ethanol was heated in a sealed steel vessel at 100 °C for 80 h. The reaction mixture was then cooled to rt and the solvent was removed in vacuo. The crude solid was thoroughly triturated with ether to give the corresponding 6-aminoquinoline (2, 5, 10 and 16) in 60, 95, 70 and 80 % yields respectively. Melting points, analytical
and spectroscopical data of 2, 5, and 16 have been previously reported.\textsuperscript{12,14}

6-Amino-7,8-dichlorohydroquinolin-4-one (10). mp > 300°C (EtOH); \textsuperscript{1}H-NMR (DMSO-\textsubscript{d6}): δ 11.65 (s, 1H, NH), 8.71 (s, 1H, H-5), 7.99 (d, 1H, J = 7.6 Hz, H-3), 6.09 (d, 1H, J = 7.6 Hz, H-2), 4.57 (s, 2H, NH\textsubscript{2}); LC/MS: 229 (M+H); Anal. Calcd for C\textsubscript{9}H\textsubscript{6}N\textsubscript{2}OCl\textsubscript{2}: C, 47.19; H, 2.64; N, 12.23. Found C, 46.88; H, 2.86; N, 12.04.

Method B: using hydrazine and 10\% Pd-C.
A suspension of 1 or 4 (12.0 mmol), 10\% Pd-C (0.50 g) and 5 mL of hydrazine monohydrate (98\%) in 50 mL of ethanol was refluxed under stirring for 2.5 h. On cooling, the catalyst was filtered off and both solvent and excess of hydrazine removed \textit{in vacuo}. The crude solid was thoroughly triturated with acetone to yield the corresponding de-halogenated 6-aminoquinoline (6 and 7) in 95 and 70 \% yield respectively. Melting point, analytical and spectroscopical data of 7 have been previously reported.\textsuperscript{12}

6-Aminoquinoline (6). mp 98-100°C (EtOH); \textsuperscript{1}H-NMR (CDCl\textsubscript{3}+DMSO-\textsubscript{d6}): δ 8.66 (d, 1H, J = 4.8 Hz, H-2), 8.56 (d, 1H, J = 8.4 Hz, H-4), 8.02 (d, 1H, J = 9.0 Hz, H-8), 7.73 (dd, 1H, J = 4.8 and 8.4 Hz, H-3), 7.50 (d, 1H, J = 9.0 Hz, H-7), 7.04 (s, 1H, H-5), 6.5 (s, 2H, NH\textsubscript{2}); MS M/Z 144 (M\textsuperscript{+}); Anal. Calcd for C\textsubscript{9}H\textsubscript{8}N\textsubscript{2}: C, 74.98; H, 5.59; N, 19.43. Found C, 74.63; H, 5.75; N, 19.22.

Preparation of 7,8-dichloro-4-ethoxy-6-nitroquinoline (11). To a suspension of 9 (1.0 g, 3.86 mmol) and 1.24 g (3.86 mmol) of cesium carbonate (99\%) in 20 mL of dehydrated DMF (less than 0.0100\% of water) under stirring was heated at 60 °C and slowly added a solution of ethyl sulfate (0.74 g, 4.8 mmol) in 6 mL of DMF. After the addition was complete, the reaction mixture was stirred for an additional 4 h, then poured into 150 g of crushed ice. The solid obtained was collected by filtration and recrystallized from acetone to yield 0.67 g (60\%). mp 123-124°C; \textsuperscript{1}H-NMR (DMSO-\textsubscript{d6}): δ 8.96 (d, 1H, J = 5.4 Hz, H-2), 8.65 (d, 1H, J = 8.4 Hz, H-4), 8.02 (d, 1H, J = 9.0 Hz, H-8), 7.73 (dd, 1H, J = 4.8 and 8.4 Hz, H-3), 7.50 (d, 1H, J = 9.0 Hz, H-7), 7.04 (s, 1H, H-5), 6.5 (s, 2H, NH\textsubscript{2}); MS M/Z 286 (M\textsuperscript{+}); Anal. Calcd for C\textsubscript{11}H\textsubscript{8}N\textsubscript{2}O\textsubscript{3}Cl\textsubscript{2}: C, 46.02; H, 2.81; N, 9.76. Found C, 45.76; H, 3.10; N, 9.50.

Preparation of 4-chloroquinolines (15 and 17). A solution of 14 or 16 (5.0 mmol) in 20 mL of phosphorus(V) oxychloride (99\%) was refluxed under stirring for 24 h. The reaction mixture was then cooled to rt and poured into 200 g of crushed ice. The resulting solution was made alkaline with 25\% aqueous ammonia solution. The crude solid obtained was purified by chromatography on silica gel with a 9:1 mixture of ether-ethanol, to give 15 and 17 respectively.

7-Amino-4,8-dichloro-6-nitroquinoline (15). (70 \%). mp 196-198°C (acetone); \textsuperscript{1}H-NMR (DMSO-\textsubscript{d6}): δ 8.88 (d, 1H, J = 5.0 Hz, H-2), 8.81 (s, 1H, H-5), 7.62 (d, 1H, J = 5.0 Hz, H-3), 7.23 (s, 2H, NH\textsubscript{2}); MS M/Z 257 (M\textsuperscript{+}); Anal. Calcd for C\textsubscript{9}H\textsubscript{5}N\textsubscript{2}O\textsubscript{2}Cl\textsubscript{2}: C, 41.89; H, 1.95; N, 16.28. Found C, 41.76; H, 1.68; N, 15.90.
6,7-Diamino-4,8-dichloroquinoline (17). (50 %). mp 168-170°C (EtOH); ¹H-NMR (CDCl₃+DMSO-d₆): δ 8.51 (d, 1H, J = 5.0 Hz, H-2), 7.24 (s, 1H, H-5), 7.22 (d, 1H, J = 5.0 Hz, H-3), 5.15 (s, 2H, NH₂), 4.78 (s, 2H, NH₂); MS M/Z 227 (M⁺); Anal. Calcd for C₉H₇N₃Cl₂: C, 47.39; H, 3.09; N, 18.42. Found C, 47.70; H, 2.87; N, 18.06.

Displacement by ammonia of chlorine atoms and ethoxy group

A solution of 1, 9, 11 or 15 (12.0-24.0 mmol) in ethanol (120-250 mL) saturated with dry gaseous ammonia was heated in a sealed steel vessel at 160 °C under stirring for 24 h (in the case of 1 and 9), 15 h (in the case of 15) and 120 h (in the case of 11). Then the reaction mixture was cooled to rt, the solvent was removed in vacuo and the solid residue recrystallized from ethanol, to give 4 (98%), 14 (87%), 12 (90 and 97% from 11 and 15 respectively). When the compound (11) was submitted to the same reaction for a shorter time (65 h) a mixture of diamine (12) in 50% yield and monoamine (13) in 40 % yield was obtained. Purification was achieved by chromatography on silica gel eluting with a 9:1 mixture of chloroform-methanol, to give in the sequence compounds (13) and (12). Melting points, analytical and spectroscopical data of 4 or 14 have been previously reported.¹²,¹⁴

4,7-Diamino-8-chloro-6-nitroquinoline (12). mp > 300°C (EtOH); ¹H-NMR (DMSO-d₆): δ 9.20 (s, 1H, H-5), 8.28 (d, 1H, J = 5.4 Hz, H-2), 7.88 (s, 2H, NH₂), 7.00 (s, 2H, NH₂), 6.49 (d, 1H, J = 5.4 Hz, H-3); LC/MS: 239 (M+H); Anal. Calcd for C₉H₇N₄O₂Cl: C, 45.30; H, 2.96; N, 23.48. Found C, 45.66; H, 3.07; N, 23.21.

4-Amino-7,8-dichloro-6-nitroquinoline (13). mp > 300°C (acetone); ¹H-NMR (CDCl₃+DMSO-d₆): δ 9.04 (s, 1H, H-5), 8.48 (d, 1H, J = 5.4 Hz, H-2), 7.53 (s, 2H, NH₂), 6.74 (d, 1H, J = 5.4 Hz, H-3); LC/MS: 258 (M+H); Anal. Calcd for C₉H₅N₃O₂Cl₂: C, 41.89; H, 1.95; N, 16.28. Found C, 46.21; H, 3.18; N, 16.01.

Preparation of acetylaminoquinolines (3 and 8). A suspension of 2 or 8 (4.5 mmol) in acetic anhydride (15 mL), was stirred to rt overnight, the resulting precipitate was filtered off, washed with water and dried, to afford in 90% respectively:

N-(7,8-Dichloroquinolin-6-yl)acetamide (3). mp 209-210°C (acetone); ¹H-NMR (DMSO-d₆): δ 9.89 (s, 2H, NH), 9.00 (d, 1H, J = 4.8 Hz, H-2), 8.38 (d, 1H, J = 8.4 Hz, H-4), 8.28 (s, 1H, H-5), 7.64 (d, 1H, J = 4.8 and 8.4 Hz, H-3); MS M/Z 254 (M⁺); Anal. Calcd for C₁₁H₈N₂OCl₂: C, 51.79; H, 3.16; N, 10.98. Found C, 52.12; H, 3.00; N, 11.33.

N-(6-Acetylamino-8-chloroquinolin-7-yl)acetamide (8). mp 253-255°C (acetone); ¹H-NMR (DMSO-d₆): δ 9.67 (s, 2H, NH), 9.20 (s, 2H, NH), 8.91 (d, 1H, J = 4.8 Hz, H-2), 8.40 (s, 1H, H-5), 8.24 (d, 1H, J = 8.0 Hz, H-4), 7.51 (dd, 1H, J = 4.8 and 8.0 Hz, H-3); MS M/Z 277 (M⁺); Anal. Calcd for C₁₃H₁₂N₃O₃Cl: C, 56.22; H, 4.36; N, 15.13. Found C, 55.90; H, 4.48; N, 14.88.
REFERENCES AND NOTES


